ABSTRACT

The US Food and Drug Administration approves generic forms of brand-name drugs if they are able to show bioequivalence, as well as standards in drug content (active drug and excipient), labeling, and manufacturing. Bioequivalence is calculated based on 3 pharmacokinetic parameters: the maximum concentration in the blood, the time at which the maximum concentration is reached, and the extent of drug absorption (the area under the concentration-versus-time curve). This article reviews the exact definition of bioequivalence, as well as the factors that affect bioequivalence and how they relate to substitution of brand-name antiepileptic drugs (AEDs) with generic formulations or substitution among generic formulations. This is a matter of serious debate because of the potentially devastating consequences of one breakthrough seizure if a patient is switched. The published studies and reports of toxicity or therapeutic failure with AEDs, although numerous, have a wide range of scientific strength and provide no clinical guidance other than to underscore the variability of patient response to generic substitution and the importance of monitoring. This article also includes highlights of a roundtable summary published by the American Pharmaceutical Association describing in detail the issues surrounding substitution of brand-name drugs with generic drugs. Highlights of that publication are discussed here and serve as a foundation for the practical implications of generic substitution of antiepileptic drugs (AEDs).

Understanding Generic Drug Approval

The use of generic drugs to replace brand-name drugs is a frequent topic among all types of healthcare professionals, especially in light of the rapidly rising costs of healthcare. Within these discussions are terms whose meanings may not be completely clear, but whose impact on allocation of resources and patient outcomes is substantial. The American Pharmaceutical Association published a roundtable summary describing in detail the issues surrounding substitution of brand-name drugs with generic drugs. Highlights of that publication are discussed here and serve as a foundation for the practical implications of generic substitution of antiepileptic drugs (AEDs).

In order for the US Food and Drug Administration (FDA) to approve a generic version of a drug, the manufacturer of the generic product must prove that the drug is therapeutically equivalent by meeting the criteria regarding the content (active drug and excipient), bioequivalence, labeling, and manufacturing, as outlined in the Sidebar. It does not have to show efficacy data.

Bioequivalence and bioavailability are similar but different terms. Importantly, if 2 drugs are bioequivalent to each other, they are equally bioavailable, but the reverse is not necessarily true. If 2 drugs are equally bioavailable, they are not always bioequivalent. In a typical bioequivalence study, 18 to 36-healthy volunteers receive a single dose of the brand-name drug and generic drug in a randomized crossover design (thus creating internal controls). After each drug is administered, blood or plasma concentrations of the drug are measured over time. Bioequivalence is based on the time course and blood level concentrations of a single drug dose.

Bioequivalence is calculated based on 3 pharmacokinetic parameters: the maximum concentration in the blood (C\text{\text{max}}), the time at which the maximum concentration is reached (T\text{\text{max}}), and the extent of drug absorption (the area under the concentration-versus-time curve...
Bioequivalence is measured by the ratio of $C_{\text{max}}$ to AUC. Of note, the FDA requires that this ratio fall within 80% to 125% of the branded drug's ratio. In fact, the actual calculation is the ratio of the mean $C_{\text{max}}$ to the mean AUC, and the 90% confidence intervals must fall within the range of 80% to 125% of the branded drug. The confidence intervals indicate that the generic drug will be absorbed to the same mean rate and extent as the mean of the innovator, 90% of the time. This means that if an individual was tested 10 times, 9 of the 10 times his/her ratio would fall within the lower and upper interval. Generic drugs are compared with an innovator drug and not with each other. As shown in Figure 1, the difference between comparing only mean values versus 90% confidence intervals makes a significant difference in determining which drugs are said to be bioequivalent. The actual differences between the mean values is smaller than –20% to +25%.

The Approved Drug Products with Therapeutic Equivalence Evaluations (aka, the Orange Book), published by the FDA, is the leading authoritative resource on the therapeutic equivalence of FDA-approved drugs. The innovator drug is listed as the reference drug. Generic drugs are rated as A, AB, or B to indicate their level of bioequivalence. An A rating indicates no known or suspected bioequivalence problems and therefore therapeutic equivalence. An AB rating indicates that any bioequivalence problems were resolved with further testing. A rating of B indicates that the drug is not considered to be therapeutically equivalent. B-rated drugs are FDA approved; however, they are not considered to be therapeutically equivalent to the innovator product. For this reason, pharmacists should not substitute brand-name drug with a generic form without obtaining authorization from the prescriber. Finally, some drugs have a BX rating, indicating that there is insufficient evidence of bioequivalence. Not all state boards of pharmacy include the Orange Book as a required reference for the pharmacy. Many pharmacists rely on the corporate office to add available bioequivalent products into the computer system. Although the pharmacist can access the information on the FDA Web site, many companies do not allow their employees to have Internet access. Hence, the pharmacist is left to rely on his/her "professional judgment."

A number of AEDs have a narrow therapeutic index (NTI, also referred to by the FDA as narrow therapeutic ratio). The NTI is defined as a less than 2-fold difference in median lethal dose (LD$_{50}$) and median effective dose (ED$_{50}$), or a less than 2-fold difference in the minimum

![Figure 1. Cases Testing for Bioequivalence](image)

This figure illustrates the US Food and Drug Administration (FDA) requirement of the ratio of mean area under the concentration-versus-time curve to mean $C_{\text{max}}$ falling within the range of 80% to 125% of that ratio for the brand-name drug. In this figure, the mean ratio is indicated by the vertical bar. The first example shows that the test drug (a generic) has 90% confidence intervals that fall outside the 80% to 125% range, and so would not be approved by the FDA. In case 2, the 90% confidence intervals are too high, extending beyond the maximum of 125% of brand-name drug. This drug also would not be approved. Case 3 shows that not only the mean ratio but also the 90% confidence intervals fall within the 80% to 125% range, so the drug would be approved.


<table>
<thead>
<tr>
<th>FDA Requirements for Therapeutic Equivalence of a Generic Formulation</th>
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<tr>
<td>1. It is pharmaceutically equivalent.</td>
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<tr>
<td>a. It contains the same amount of active drug in the same dosage form.</td>
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<tr>
<td>b. It meets compendial standards for purity, strength, identity, and quality.</td>
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<tr>
<td>2. It is bioequivalent.</td>
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<td>3. It is adequately labeled.</td>
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FDA = US Food and Drug Administration.
toxic concentrations and minimum effective concentrations in the blood as well as whether safe and effective use of the product requires careful titration and patient monitoring. Because some AEDs are considered to have an NTI, the use of their generic forms is under closer scrutiny. There has been criticism that the FDA requirements for showing bioequivalence are not adequate for NTI drugs, however, the FDA requires that NTI drugs meet the same guidelines.

FACTORS AFFECTING DRUG BIOEQUIVALENCE

Numerous factors affect a drug’s bioequivalence—both intrinsically (within the drug) and extrinsically (within the person receiving the drug). Intrinsically, the drug’s solubility in water will affect bioavailability, as will the absorption pharmacokinetics. The chemical structure of the drug as a free acid or salt, the dosage form (capsule, tablet, or suspension), content by weight (eg, divalproex vs valproate), and other formulation components (excipients, binders, fillers, lubricants) can have a large impact on a drug’s bioavailability and therefore bioequivalence compared with the brand-name drug. Drugs that exhibit nonlinear pharmacokinetics also make bioequivalence more complicated. And, as will be discussed below, some drugs are prone to spoilage during storage, which can affect bioequivalence.

Extrinsically, the physiology of the patient may also affect bioavailability in many ways. The transit time in, pH of, and absorption rate from the gastrointestinal tract can greatly impact not only the amount but also the time to peak blood concentrations. Metabolism by the liver and clearance by the kidneys can be of greater or lesser efficiency depending on each individual patient. Bioequivalence studies are performed in healthy, generally young adult volunteers. It is unknown if data can be extrapolated to other patient populations, such as young children and elderly patients.

The presence of food in the stomach can also alter bioavailability for some medications. In the bioequivalence studies required by the FDA, the drugs are taken on an empty stomach, but the FDA mandates that controlled-release (and many immediate-release) dosage forms undergo a food study (ie, taking the drug with a high-fat meal). Few generic AEDs are currently available on the market. They include: phenytoin, carbamazepine, valproate, and gabapentin. There are a number of extended-release formulations of AEDs that do not have generic formulations including Tegretol XR® and Carbaltrol® (both carbamazepine but not interchangeable drugs), Phenytek® and Dilantin® (phenytoin), and Depakote ER® (divalproex sodium). As patent protection begins to expire, additional generic AEDs will be entering the market.

The discussion of whether to use generic drugs is contentious in the epilepsy community because the consequences of poor bioavailability are serious and potentially life-threatening for the patient. Many patients are tenuously balanced between seizure control and toxicity. Switching manufacturers can upset that balance. The American Academy of Neurology (AAN) published a consensus statement on generic substitution for AEDs roughly 15 years ago. It is currently being updated. Nonetheless, the report from the Therapeutics and Technology Assessment Subcommittee noted that “Nonequivalence can have very serious effects. Decreased serum drug concentrations can cause breakthrough seizures, and increased concentrations can lead to toxicity. Breakthrough seizures in well-controlled patients with epilepsy can result in serious injury, and can injure or kill others if they occur during driving. Drug toxicity can lead to discomfort, injury, or poor job performance.” All of these adverse effects may lead to unnecessary clinic or emergency department visits and even hospitalization. “The overall cost to society of breakthrough seizures or drug toxicity may outweigh any economic incentive for mandating generic substitution.” Importantly, breakthrough seizures may result in the loss of driving privileges and other social ramifications that can cause severe hardship. The newer AEDs that have entered the market since 1993, such as gabapentin, topiramate, lamotrigine, levetiracetam, zonisamide, and oxcarbazepine, do not have as narrow of therapeutic ranges as compared with the older AEDs, but caution should still be exercised. As patents expire, the newer AEDs will become available generically, and if individuals are switched to the generic formulation, they will need to be monitored for changes in seizure control or toxicity.

PUBLISHED STUDIES COMPARING GENERIC VERSUS BRANDED AEDS

Of the AEDs, phenytoin and carbamazepine have the most complex factors potentially influencing bioavailability—poor solubility in water, NTI, nonlinear pharmacokinetics, and age-related pharmacokinetics (ie, studies in adults may not always translate to the pediatric population). Published studies comparing
generic with branded forms of AEDs are essentially limited to phenytoin, carbamazepine, and valproate, and are scattered over several decades. Phenytoin suspension may be poorly absorbed in children, and the bioavailability of gabapentin in children is about half that in adults. There are no published data available about the use of generic gabapentin in persons with epilepsy and it is unknown if there will be complications with its use.

**Phenytoin**

Phenytoin can be a difficult drug to manage, given its nonlinear, Michaelis-Menten kinetics. As the dose increases, there are usually greater than proportional increases in blood concentrations due to saturable metabolic enzyme pathways. Chen et al and Hodges et al compared generic versus branded forms of phenytoin in 18 adults and 19 children, respectively, with epilepsy. Although there were differences in the blood concentrations associated with the different formulations, it was not thought to be clinically significant. In the Hodges study, there were no differences in seizure frequency; it was not measured in the Chen study.7,8 Mikati et al studied 10 adult patients with well-controlled seizures in a 6-month, randomized, double-blind, crossover study of a generic versus brand-name extended-release phenytoin.9 Significant differences in predose steady-state total and free phenytoin concentrations were found between the 2 study drugs (19.3% and 22.5% higher, respectively, with generic drug), but the potency also varied between the 2 lots in the same direction. There were no statistical differences in adverse effects. The authors indicated that the low seizure frequency and small number of patients prevented a meaningful comparison of seizure frequency, but that most patients were “very well controlled.”9

Recently, Burkhardt et al reported on 8 adult patients whose seizure rates increased enough to require intervention when the patients were switched from brand-name to generic phenytoin (extended capsules). The mean total steady-state serum concentration decreased 30% during generic administration but returned to pre-generic values when brand-name phenytoin was reintroduced.10 It is known that patients may routinely take phenytoin with a meal to improve compliance or reduce gastrointestinal upset. Wilder et al compared 100-mg phenytoin capsules with the brand-name version of the capsule formulation in 24 healthy subjects in conjunction with a high-fat breakfast (i.e., 2 eggs scrambled in butter, 2 pieces of white toast spread with 2 teaspoons of butter, 2 ounces of hash brown potatoes, 2 pieces of bacon, and 4 ounces of whole milk). The results showed a 13% decrease in bioavailability with the generic formulation after the high-fat meal compared with the brand-name form. Extrapolation based on pharmacokinetic data from 30 persons with epilepsy revealed that the decrease in bioavailability would result in a median 37% decrease (range 19%-58%) in plasma phenytoin concentration. In 46% of patients, the plasma concentration would fall below the reference range of 10 µg/mL to 20 µg/mL. Therefore, if branded was substituted for the generic product, the 102% increase in plasma phenytoin concentration would render 84% of those patients with concentration above the reference range, possibly inducing side effects.11

**Carbamazepine**

Carbamazepine is challenging to dose due to its own autoinduction and concentration-related side effects. As the dose increases, there are often less than proportional increases in blood concentration. Hartley et al evaluated steady-state serum concentrations of carbamazepine in 12 children receiving generic versus brand-name carbamazepine (100-mg and 200-mg tablets). Although the in vitro dissolution rate was higher with the brand-name form, the authors noted that the breakthrough seizures and higher incidence of neurological side effects with generic carbamazepine could not be accounted for based on bioavailability or pharmacokinetics including the epoxide metabolite, which were similar between the 2 drug formulations.12 Welty et al described 2 cases of lost seizure control associated with generic substitution of carbamazepine tablets.13 Decreases in serum concentration of carbamazepine were 46% in one patient and 28% in the other during substitution. Importantly, one of the patients was a 21-year-old woman who had been seizure free for 5 years. She was switched to generic and became pregnant at approximately the same time, so it is difficult to determine if the worsening of her seizure control was due to generic substitution or alterations in pharmacokinetics attributed to pregnancy. She was not able to regain seizure control when brand-name drug was resumed.13 Gilman et al also described 2 pediatric cases of carbamazepine toxicity (both children were 6 years old), resulting from substitution of generic carbamazepine tablets. Toxicity manifested as brief behavioral changes, lethargy, slurred speech
(Patient 1), and headache, ataxia, pale complexion, morning vomiting, and nystagmus (Patient 2). Maximum serum concentrations were increased by 22% and 41%. When the serum concentrations were returned to normal, the children were asymptomatic.14 Oles et al performed a randomized, double-blind, crossover therapeutic bioequivalence study of generic versus brand-name carbamazepine tablets. Even when differences in AUC and Cmax were up to 20% between the formulations, there were no statistical differences between the 2 drugs in terms of bio- or therapeutic equivalence. The seizure frequency was similar with both drugs.15 Silpakit et al, in another double-blind, randomized, 3-phase crossover study in 18 patients, compared 3 generic formulations with brand-name carbamazepine tablets. The results showed no significant difference in pharmacokinetic parameters among the 4 drugs, but only 2 of the 3 generic forms were able to maintain AUCs within the range of 80% to 120% of the brand-name drug, which were the parameters for this study.16 Aldenkamp et al compared brand-name with 2 generic forms of carbamazepine tablets (all with different dissolution rates) and found no differences in cognitive impairment or pharmacokinetic parameters among the 3 drugs. This was a randomized, open-label, observer-blinded, crossover study in 12 patients.17 In order to address concerns about bioequivalence studies using single doses, Yacobi et al studied 3-times-a-day dosing of 200-mg tablets of carbamazepine (branded vs generic) in 32 subjects (28 of whom completed the study). Pharmacokinetic parameters and measures of fluctuation at steady-state dosing were similar for both products, with 90% and 95% confidence intervals falling within 90% to 110% of those for brand-name drug.18

**Valproate**

The data on valproate are limited. Two case reports discuss breakthrough seizures and gastrointestinal side effects during substitution with generic valproic acid. In one case Depakene® (valproate) was substituted with generic valproate resulting in a breakthrough seizure. In the second case, Depakote® (divalproex sodium) was substituted with generic valproate resulting in significant gastrointestinal side effects.19,20 Divalproex sodium dissociates to valproate in the intestinal tract, but the drug is significantly better tolerated in terms of gastrointestinal side effects than generic valproate. There is currently no generic product available for divalproex sodium. Vadney performed an 8-week, open-label study of 64 mentally retarded subjects with epilepsy and found no statistically significant changes in seizures or blood concentrations between the 2 valproate formulations.21

**Recalled formulations**

Interestingly, 2 studies have analyzed recalled versions of generic drugs, to assess their bioequivalence. Rosenbaum reviewed charts of outpatients from the Bronx Veteran’s Affairs hospital who had been switched to a generic formulation of phenytoin, but switched back to brand-name phenytoin 5 months later, when the generic formulation was recalled. The serum phenytoin concentrations were 22% to 31% lower during the period of generic use compared with concentrations during brand-name phenytoin use. It was discovered that, although the generic formulation met FDA standards at the time of manufacture, it underwent a change in dissolution characteristics while in storage (ie, in the medicine cabinet), presumably altering the characteristics that control dissolution and perhaps therapeutic equivalence.22 Similarly, Meyer et al evaluated 3 lots of generic carbamazepine tablets (200 mg) that had been withdrawn from the market. A total of 53 lots were withdrawn due to several reports of clinical failures as well as observed changes in the dissolution characteristics of the drug. Not surprisingly, the wide ranges of bioavailability and in vitro dissolution rates were outside the 80% to 125% requirement compared with brand-name drug.23

The quality of all these generic versus brand-name drug studies range from case reports to small randomized trials. Meyer points out several potential reasons for the paucity of examples of toxicity or therapeutic failures from generic substitution. For example, the patient(s) may not have been compliant or the wrong drug or incorrect dose might have been taken. The patient may also have continued to take both products. The patient(s) may have had a change in disease process or physiology, or experienced a drug-drug or drug-nutrient interaction. Finally, a therapeutic failure is difficult to prove without rechallenge. In most cases of patients with epilepsy, the dangers posed by a rechallenge may not be acceptable or even considered unethical.

Despite the numerous studies discussed here, none of the study results can be extrapolated to generic forms that were not included in the study. For example, if the confidence interval for the mean AUC value is small, it is theoretically possible for the average patient to have an almost 50% increase in serum con-
centration when switching from a generic drug with low bioavailability (80% of brand name) to one with high bioavailability (120% of brand name). Thus, any comparative study can only be used to evaluate that particular generic formulation. It is difficult, therefore, to ascertain any consistent message from these studies, other than a reassertion that individual variability is an important factor in whether generic substitution will be successful in any given patient and that blood concentration monitoring for an NTI medication is critical, but may therefore negate any cost advantages of a generic AED.

**DECISION MAKING IN DISPENSING GENERIC VERSUS BRANDED DRUGS**

Although the pharmacist may not be involved in determining which drug is prescribed, it is important to understand the many factors that are considered in prescribing an AED for a person with epilepsy. These same factors are considered when the pharmacist is faced with the decision of whether to switch to a generic form of the AED. As shown in Figure 2, the factors influencing AED choice are drug-, disorder-, and patient-related. They include efficacy and safety, acquisition cost, requirement for monitoring, possible drug interactions, patient preference/financial resources, reproductive considerations, compliance, type of epilepsy, concurrent medical conditions, and clinician familiarity with the AED.

Some states require automatic substitution of a drug if an approved generic form is available. In a survey, Wilner found that neurologists tend to greatly underestimate the frequency of short-acting carbamazepine substitution to generic.

There are certain advantages to switching to generic formulations beyond cost savings. Generic names are standardized, which helps to avoid confusion among some brand names. Also, generic choices can help a pharmacist control the stock of their pharmacy by choosing specific formulations.

The risks of switching from branded to generic AEDs or among generic AEDs can be serious and unique to epilepsy. The most frequent and dangerous risk is of breakthrough seizures. Even if the generic form may be as effective as the brand name in long-term control of seizures, breakthrough seizures can occur during the switch. As mentioned by the AAN Task Force, seizures have far-reaching ramifications such as possible injury or death (to the patient or others), cognitive impairment, extra office/emergency room visits, and loss of earnings and driving privileges for the patient.

If the pharmacist is required to or chooses to switch to a generic AED, particularly phenytoin or carbamazepine (due to their NTIs), the prescriber needs to be informed and possibly consulted. Patients should also be informed and educated about generic substitution. Most patients may be resistant to substitution, even with the lower costs, especially if they have been well controlled on their current AED regimen. The pharmacist should be prepared to provide additional information to the patient on the advantages (primarily cost) and possible complications (breakthrough seizures) of switching to the generic formulation.

**CLINICAL MONITORING WITH GENERIC AEDS**

If a patient is switched to a generic AED, close monitoring is warranted for the first few months of...
therapy to determine if there are changes in clinical efficacy or signs of toxicity. Efficacy can change depending on the absorption of the drug. If less drug is absorbed than with the brand-name product, there is less medication available systemically, which may result in a return of seizure activity or an increase in seizure frequency. If more drug is absorbed than with the brand-name drug, dose-dependent side effects, including central nervous system side effects such as trouble with vision, balance, and increased fatigue, may occur. Although there are reference ranges for most AEDs, each individual patient may respond differently to therapy based on their own unique physiology and may be precariously balanced between efficacy and toxicity. Thus, some patients may be particularly intolerant of switching formulations or manufacturers (ie, from brand to generic).

If indicated, blood concentrations should be checked when the patient has been on the new formulation long enough to reach steady state, generally 5 half-lives. This time period may be difficult to predict due to variable pharmacokinetic parameters. For example, phenytoin may take 1 to 4 weeks, due to dose-dependent clearance while carbamazepine may take 3 days to 1 week to reach steady-state concentrations, due to autoinduction.

Whereas there are general reference ranges, each patient should be monitored individually. In any case of switching to a generic formulation, the same manufacturer should be used. Similarly, switching between generic forms of the same drug is the same as switching back and forth between generic and brand name. Patients may require dose changes with a change in manufacturer. So, the same risks and monitoring requirements apply. Given the serious risks with switching AEDs, consistent use of the same formulation and manufacturer is necessary. It remains to be seen if switching patients to generic AEDs is cost effective, as additional costs incurred with laboratory tests and possible changes in seizure frequency may nullify the cost advantage.

CONCLUSIONS

The debate over substitution of brand-name drugs with generic formulations is a serious one, especially with regard to AEDs. Those with epilepsy do not have the luxury of “trying” a generic formulation if there is any risk of a breakthrough seizure or toxicity. Although some states require substitution with a generic formulation if it is available, the pharmacist can maintain some control over this situation by alerting the prescriber physician to the mandated substitution and discussing with them the associated risks. The pharmacist must also educate the patient on the risk of breakthrough seizures and the implications for the patient’s life (ie, driving privileges, potential for injury, hospitalization, physician visits). Although this requires additional effort on the part of the pharmacist, the benefits of continued well-controlled epilepsy with the same brand of drug may outweigh the monetary savings and morbidity (and perhaps mortality) costs for both the healthcare community and the patient with generic substitution. If generic substitution occurs, the same manufacturer of the generic form should be used throughout treatment to avoid the same bioequivalence issues in changing between generic drugs as between generic and brand-name drugs. The FDA stands strongly behind its requirements for therapeutic equivalence and many generic forms are used every day, safely and effectively. However, AEDs and other drugs with NTIs may require closer scrutiny and more stringent criteria. Currently available data on generic forms of AEDs are very limited.

REFERENCES


